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Introduction

The principal objective of this research is the development of the combination of hyperthermia (HT) and high dose rate (HDR) brachytherapy as a therapy for locally advanced, recurrent prostate cancer after failure using front line external beam definitive radiation therapy (EBRT). We had previously developed a system for low dose rate systems (LDR), however technological advances in HDR systems make the application of LDR essentially obsolete. There are several fundamentally different aspects to HDR practice and dosimetry, which render the LDR technology developed here obsolete as well. As a result the first three tasks in the statement of work are the development of a new template system, new software to control power deposition in the tumor and phantom testing before beginning patient treatment. As is demonstrated in the body of this report all three tasks have been completed on schedule. The new HDR template design differs radically from the older LDR system is easier to set up and more comfortable for the patient. The software was completely re-written to accommodate the fundamentally different HDR dosimetric approach. The combination of the hardware and software was then extensively tested on phantoms. Once satisfied that the system was safe for human application one patient was treated in accordance with the approved protocol. Finally work was initiated in the translational aspects of applying controlled gene therapy which will consist of the stress (heat and radiation) activation of the genes coding for cytotoxic molecules whose expression is activated by heat and ionizing radiation

Body of Report

Task 1 Complete the ongoing constructions of an electronic template interface compatible with HDR brachytherapy and hyperthermia systems, permitting simultaneous operation.

Task 1, as described in the statement of work was completed on schedule and has resulted in a much improved template design both in terms of setup complexity, ease of use during the procedure and patient comfort. The principal component is a new flexible thin (0.050") circuit assembly which, while being very flexible, has proven to be remarkably durable as well. In order to mount the stainless steel needles required for heating and radioactive source insertion plastic components are mounted on top of and underneath the flexible circuit foil. The design of these Delrin components is detailed in Figure 1 which gives the overall design parameters of the HDR template. There are 59 locations for hyperthermia-brachytherapy needles and 48 dedicated positions for thermometry track insertion. A cross sectional diagram of a brachytherapy/hyperthermia needle, once inserted into the template is shown in Figure 2. When the screws holding the template together (see Figure 3) are tightened the conductive O-ring is compressed making contact with the needle and a conductive masked portion of the flexible circuit foil. The foil contact is in turn connected to one of the power connectors which are then connected to the computer system which controls power input to the template based on measured temperatures from the embedded thermometry.

The overall dimensions of an assembled template (see Figure 3) are 1.888 inches (4.8 cm) high and 2.36 inches (6 cm) wide. The flexible circuit foil can be bent at up to 90 degrees providing a considerable improvement in flexibility over previous versions of the LDR template (see Figure 5). Prior to beginning an implant procedure all of the components in Figures 3 and 4 are gas sterilized since all implants are carried out in a sterile environment in a special suite in the inpatient area of the Radiation Oncology Department.

Figure 4 shows a close up photograph of a needle assembly, which corresponds to the drawing of Figure 2, as well as a thermometry catheter. Hyperthermia/brachytherapy needles are assembled during the implant procedure once the length of the protective insulator is known. It's length, determined by real time ultrasound and C-arm radiographic imaging, corresponds to the distance from the template to the proximal aspect of the tumor and can vary from needle to needle

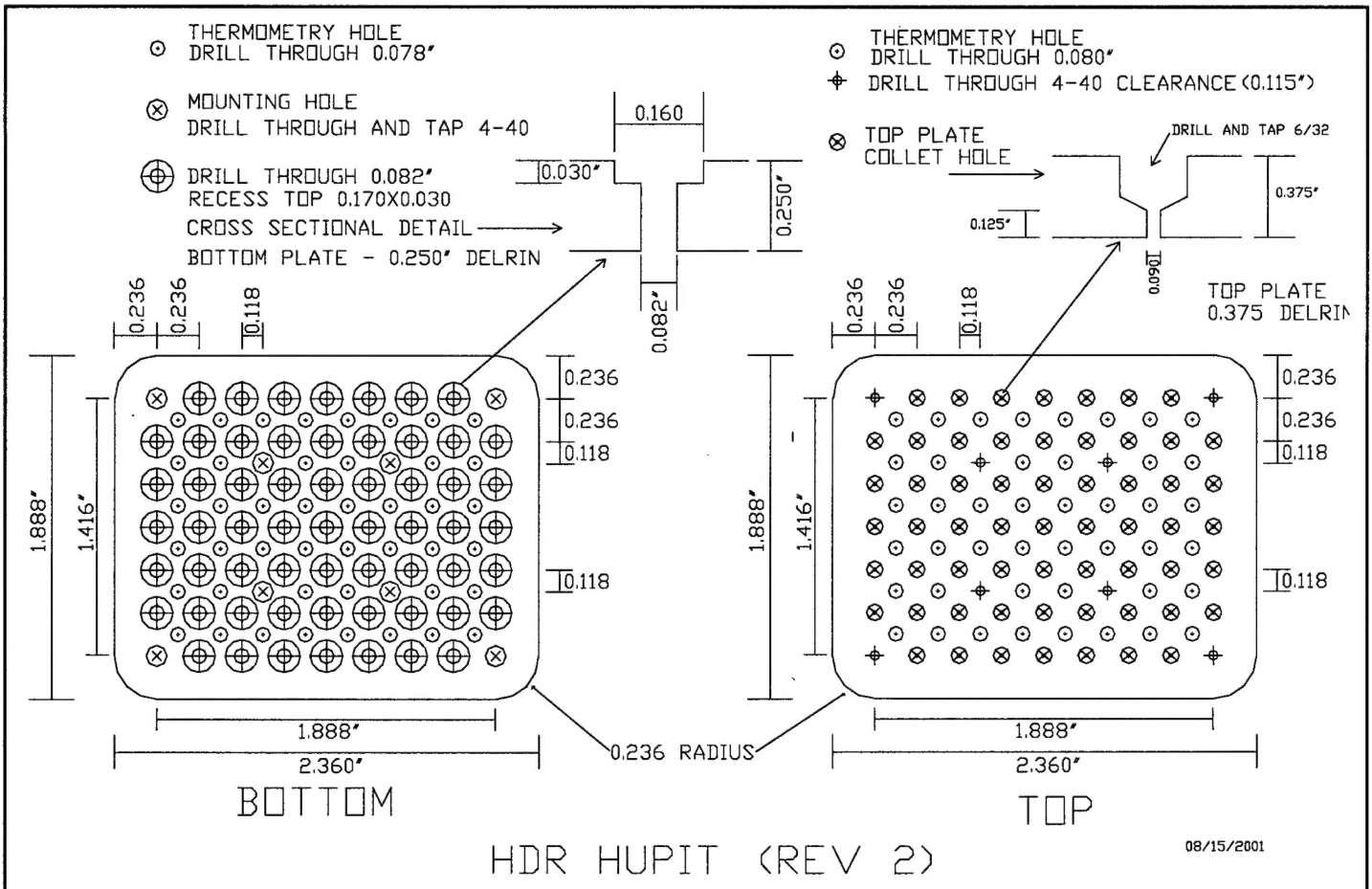

Figure 1. Schematic drawing of the template top and bottom plastic components. Dimensions are shown in inches for machining purposes. All needle separations are 6.0 mm in both horizontal and vertical directions. There are 59 positions for heating and brachytherapy sources and 48 dedicated positions for thermometry track insertion.

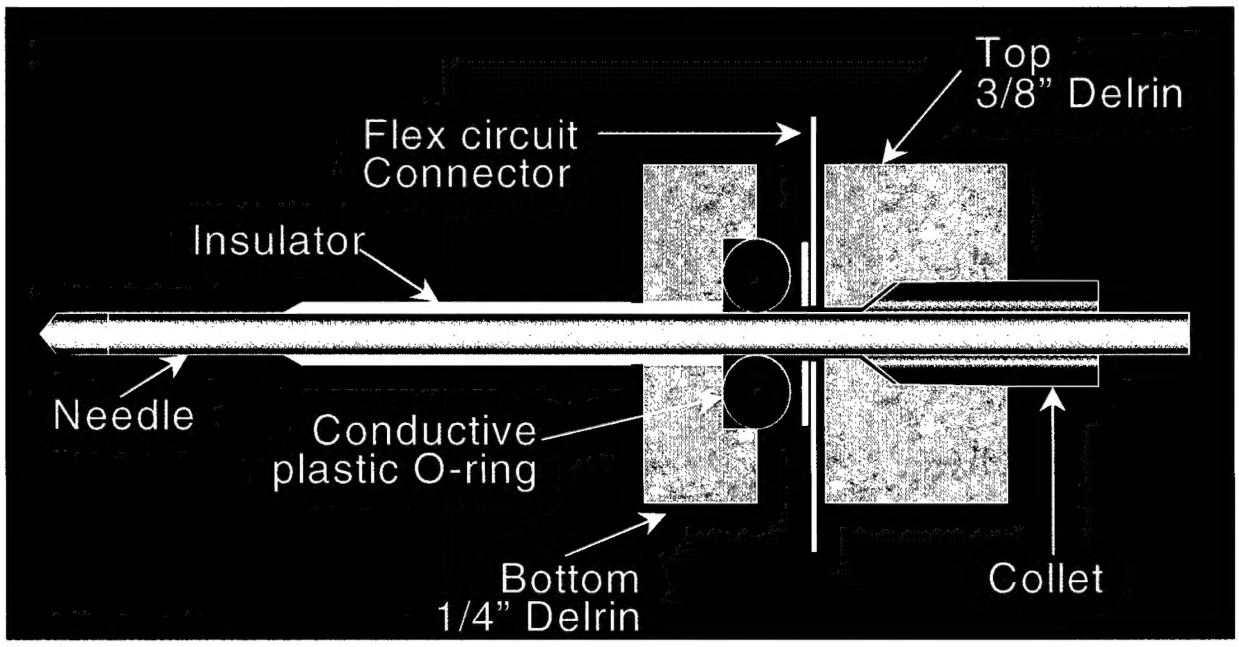

Figure 2: Cross sectional drawing of the needle design described in the text.

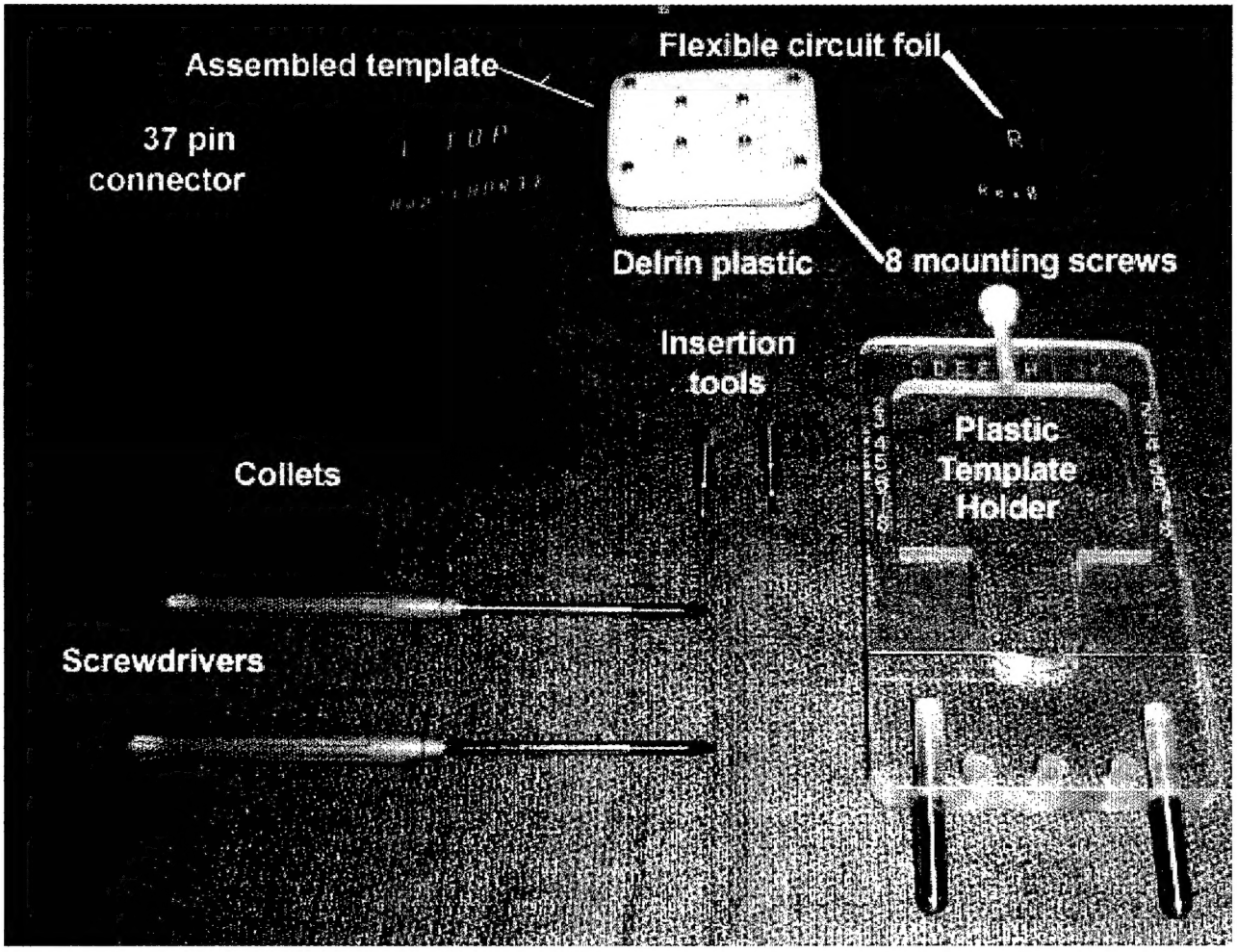

Figure 3: Assembled template and accessories. An assembled template is shown at the top of this figure, which is comprised of two connectors and the flexible circuit foil for attachment to the computer system for power control input and the two plastic components. The holes for the brachytherapy/hyperthermia needles are unique in that these needles cannot be inserted inadvertently into a thermometry hole. After the implantation of all brachytherapy/hyperthermia needles (usually 12-25) unused holes can be used for thermometry catheters in addition to the dedicated thermometry holes. The use of Delrin for the plastic template components represents a second-generation template. The original design used Lucite, which tended to crack after extended use probably as a result of cleaning fluids, gas sterilization and slightly non-uniform tightening of the template screws. During the implant procedure the template itself is mounted into the plastic template holder which in turn is mounted onto the real time ultrasound unit providing a fixed reference while inserting needles and thermometry catheters. Brachytherapy/hyperthermia needles (Figure 4) are assembled during the implant procedure with a custom insulator placed on the needle to protect tissues intervening between the surface of the template and the proximal aspect of the tumor. The template is designed such that when the eight clamping/tightening screws in the template are loose the needle with insulator installed can pass through but cannot come back out. Prior experience with LDR templates demonstrated that the insulators are an essential feature to protect the tissues of the perineum, decrease pain and improve patient tolerance. The actual thermometry devices (usually consisting of 5 discrete points at 1 cm. separation) are inserted later in the patient's room at the beginning of the first hyperthermia session. The number of thermometry catheters placed is expected to vary from 4 to 8 depending on the implant, and up to 32 sensors can be implanted in these catheters. All components shown here, and in Figure 4 below, are gas sterilized prior to an implant procedure

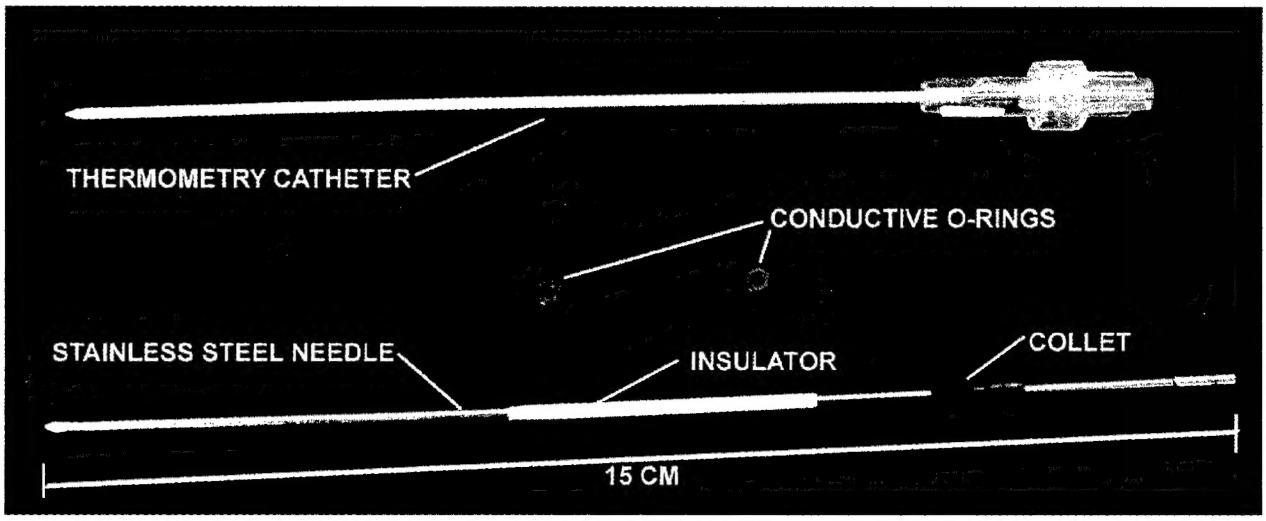

Figure 4: Needle assembly and thermometry catheter. The length of both components shown is 15 cm but they are available in 12, 18 and 21 cm lengths as well.

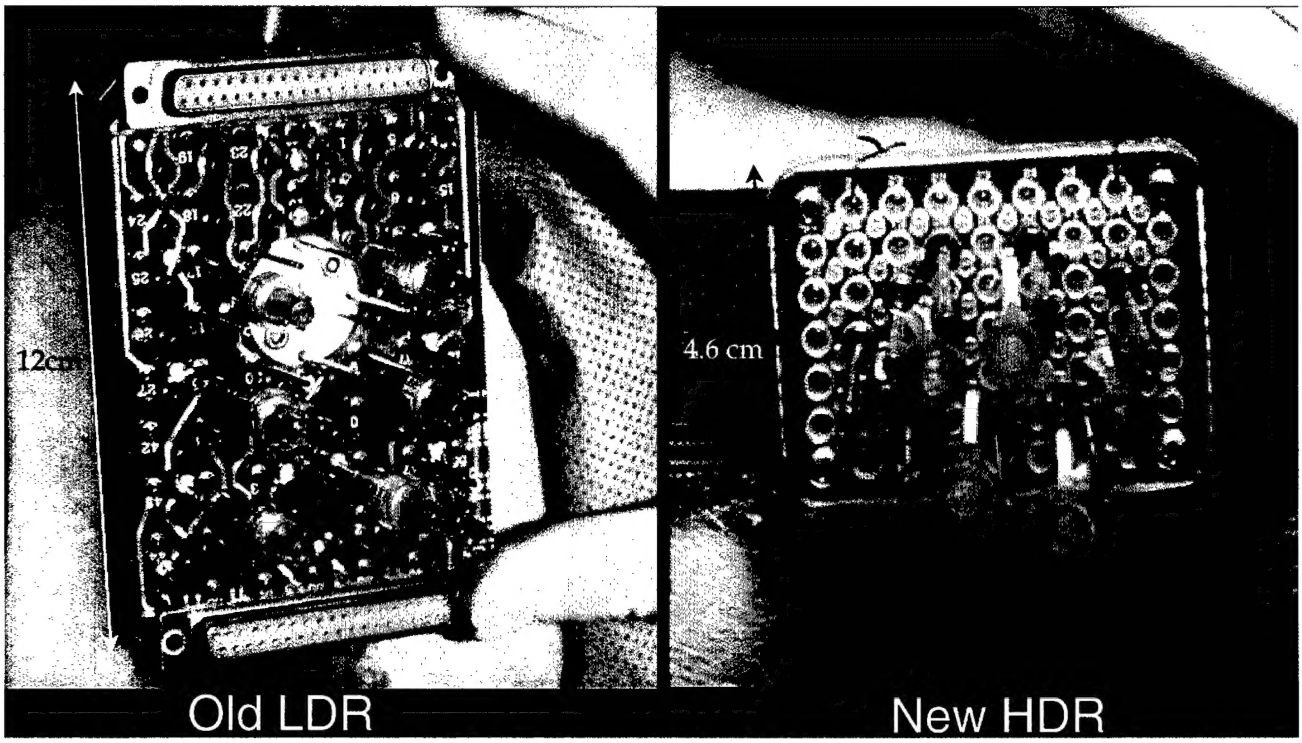

Figure 5: Photographs of old LDR and the new HDR template in place in patient therapy. The "New HDR" template shown here is made of Lucite rather than the Delrin design described above. Testing showed a tendency of the Lucite components to fail (crack) after extensive use possibly due to repeated cleaning, sterilization procedures and non-uniform tightening. The Delrin components show no such tendency and will be used for all future procedures as a precaution since the templates are designed and intended for multiple use. Only the thermometry catheters are discarded.

Task 2. Complete the ongoing development of the computer code required to effectively drive the "random placement" needle patterns associated with current HDR brachytherapy practice.

A re-write of the software was accomplished during year one although it is almost a certainty that software fine tuning will be an ongoing task as more patient treatment experience is accumulated. There are three principal components to the overall software package:

1) A temperature server (TS) program that acquires temperature data and supplies this data to any other program that requests it. Practical factors require that this program run on a computer be located in close proximity to the patient. This program has no user interface and operates in the background.

2) A power server (PS) program that monitors temperatures supplied by the TS program and alter power deposition patterns according to these temperatures, parameters of the power control algorithm and information supplied to it by the master control (MC) and monitoring program. This program has a minimal user interface.

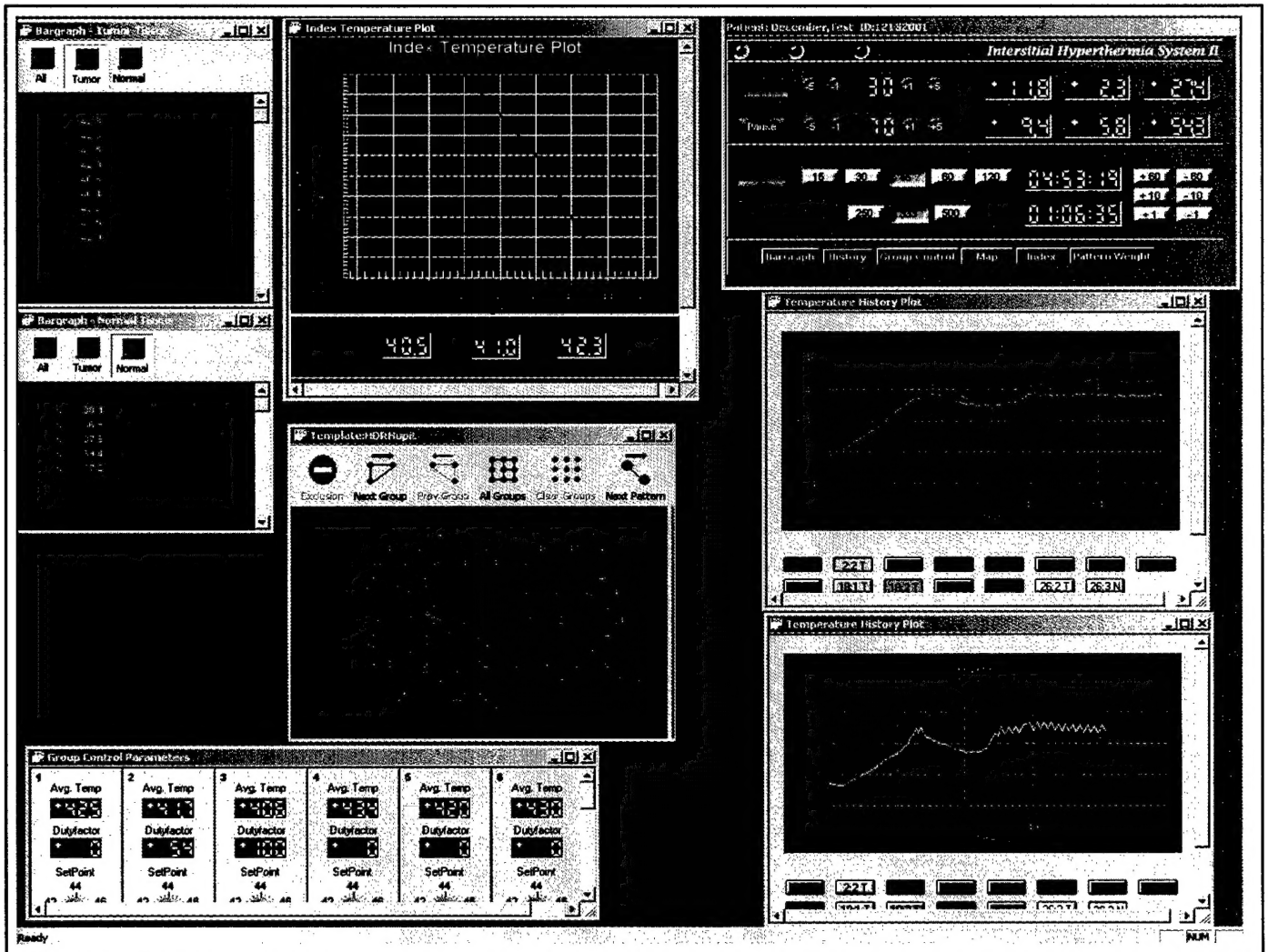

Figure 6: Screen images of the master control and monitoring program (MC) operating on a test phantom as shown below in Figure 10. Various display panes are visible including bar graphs for tumor and normal tissues (upper left), index temperature plot (upper center) system control panel (SCP, upper right), Time vs. temperature plots for various sensors (lower right), needle group control panel (lower left) and template image with current power deposition paths. All displays, except the SCP, are optional and can be activated or deactivated at the operator's convenience. Screen arrangement is also an operator preference and can be altered at any time. A different arrangement is shown in Figure 7 below.

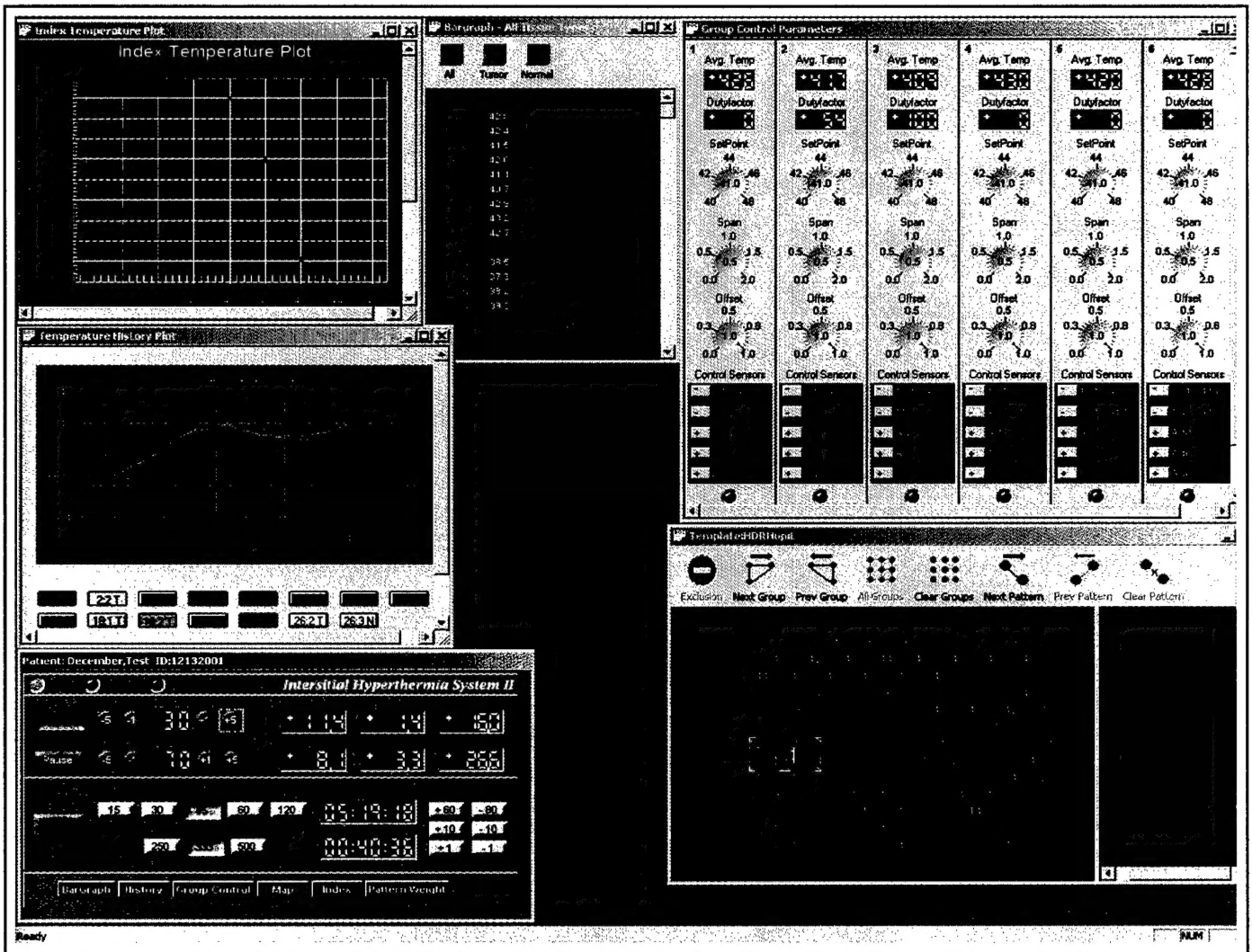

Figure 7: Screen capture of an alternate display arrangement to that shown in Figure 6 taken on the same phantom at a different time. At the upper right the complete group control panel (GCP) is shown. This control pane permits alteration of the power control algorithm parameters for each group of needles. In this particular case there are six groupings of needles. Individual needles may be members of any number of groups and groups can consist of as few as two needles. This grouping and control arrangement is essential to controlling power adequately to the essentially random spacing and patterns used in typical HDR implants. The implant pattern is determined by optimizing the brachytherapy dose distribution. No alteration of the pattern is done to accommodate hyperthermia administration although we anticipate that it may be necessary to add one to three needles to some implants to optimize hyperthermia as well.

3) The third software component is the master control (MC) and monitoring program whose output/interface is shown above in Figures 6 and 7. It is this component that reads the setup files and passes along all of the necessary information to the other two components. This program also directly controls the other two programs and acts as the overall treatment interface. It is the only program with which operators may interact during a treatment session.

There are usually two computers operating during a treatment session. The first is located in the patient's room adjacent to the patient's bed and always has the TS and PS components running at that location. Although it is possible to operate all three components on that computer, the MC component is usally operated there for only the first few minutes of the treatment session and subsequent control is transferred to a computer located in the Radiation Therapy (XRT) treatment in the hospital. It is also possible to monitor and control a treatment session from either the Cancer Center or the research laboratories as desired. It is also possible to use the dial facility in the research laboratories to access session information remotely but at

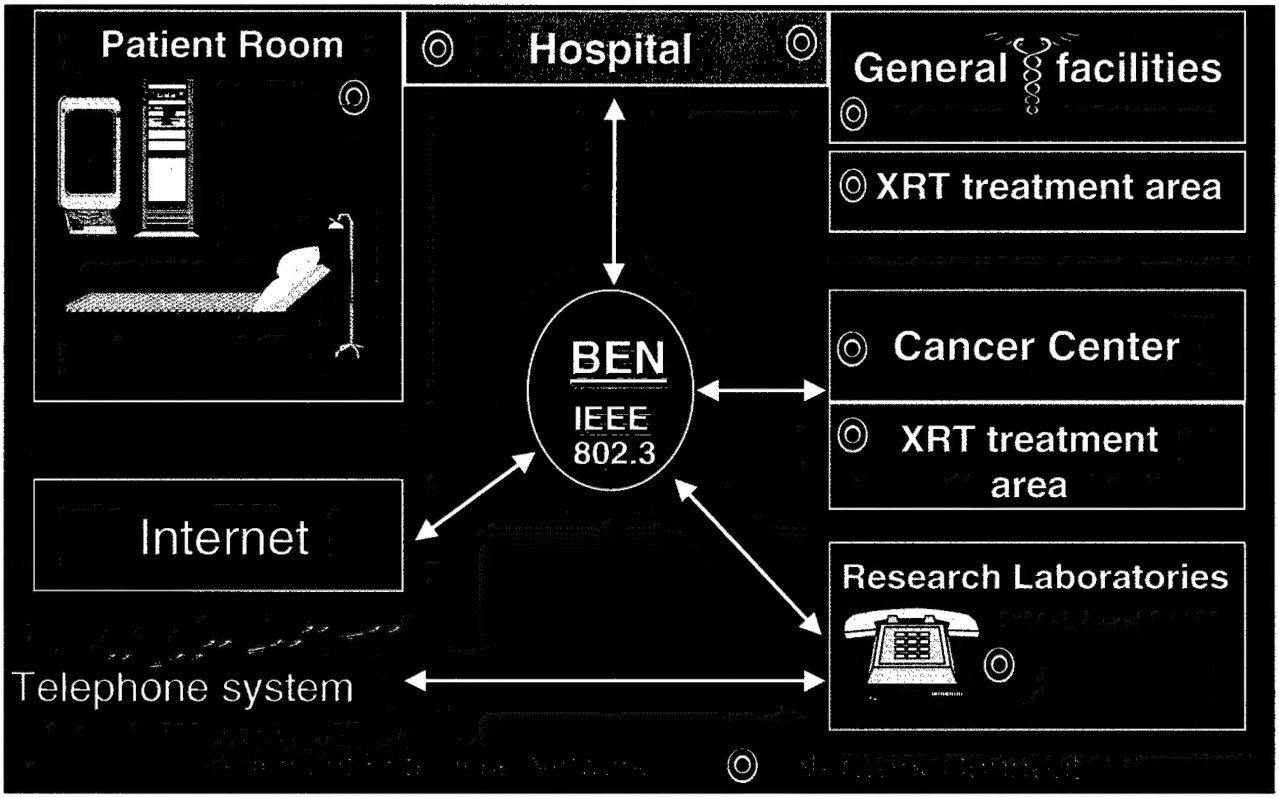

Figure 8: Diagram of the hospital network setup used to control and monitor therapy sessions. Extensive testing has shown that a control command (e.g. START, PAUSE, STOP, etc.) can be sent from the MC program and carried out by the PS program from anywhere on the network in less than 0.010 seconds.

present control of a therapy session is prohibited by this route. Direct internet access in also prohibited at this time for security reasons. All communications between programs is accomplished using a proprietary protocol working over the TCP/IP network communications protocol. This protocol is known only to those developing the software and is not published providing a very secure environment in which to control therapy.

There are two key safety features built into the hardware and software to prevent loss of control and potential harm to the patient. The first is a timing circuit built into the electronics controlling therapy. This circuit, configured as a re-triggerable one shot, operates independent of all other power generating circuitry. The computer running the PS software, which contains the control and power generation circuitry, must execute a specific set of instructions every 1.2 seconds to retrigger the timer. If this instruction set is not executed, the timer shuts down the solid state relay providing line power to the power generation circuitry, effectively "pulling the plug" on the system. This feature prevents PS program lockup and loss of positive control of hyperthermia power generation from being a potentially harmful occurrence. The second set of safety features protects against communications failures. The MC program must send a communication packet to the PS program every 60 seconds. If this does not happen the PS program will automatically enter a PAUSE state (power output to zero) and wait another 60 seconds. If the second 60-second period passes without communications the PS program shuts down completely. Additionally, the PS program will shutdown if the TS program has not sent temperature information within 30 seconds of the programmed intervals for temperature reading, usually one to five minutes. If this happens the MC program will be informed of the shutdown. All of these features have undergone extensive testing as part of Task 3 of the statement of work. All of the programs and hardware operate in a "fail safe" mode. If there is any hardware failure, such as a cable disconnect, or any communications, computer or program failure the result will be, at minimum, the shutdown of the power generation circuitry. These

features can occasionally be inconvenient for the radiation therapists administering therapy but ultimately protect the patient against the potentially harmful effects of such failures.

Task 3. Test the system on phantoms that are constructed to mimic patients that have undergone HDR prostate treatment and estimate how effectively it will generate the desired hyperthermia heating patterns.

This task required several months and effectively comprised several iterations through tasks 1 to 3. The test setup, which is identical to patient therapy except for replacement of the phantom with a patient, is shown in Figure 9 below. Figure 10 is a close up photograph of the phantom itself, which was filled with a polyacrylamide gel formulated to have tissue equivalent conductivity to simulate actual treatment.

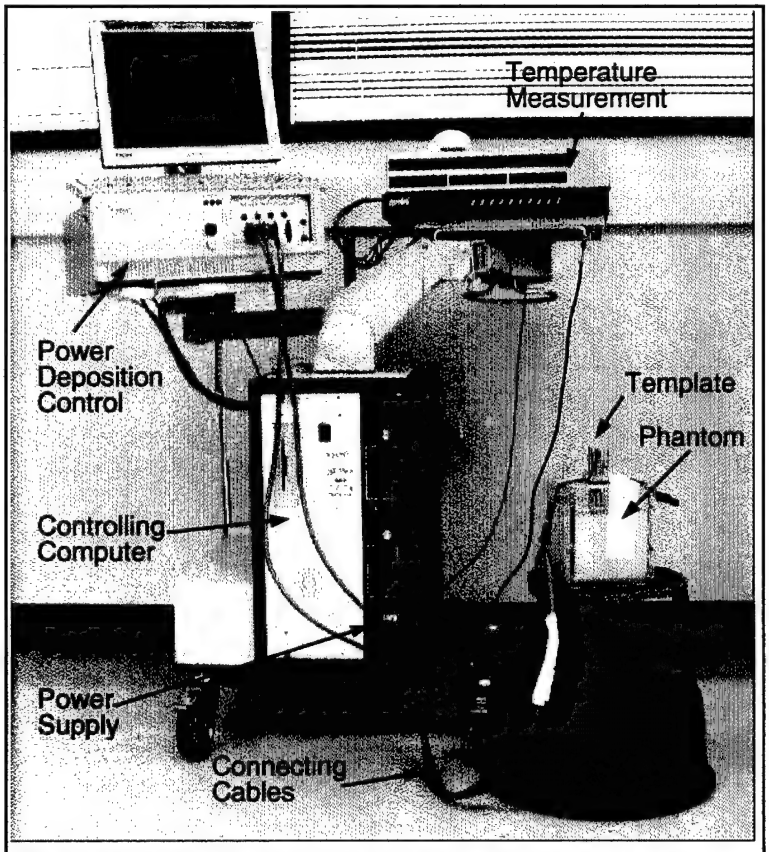

Figure 9: System setup using a phantom for test purposes.

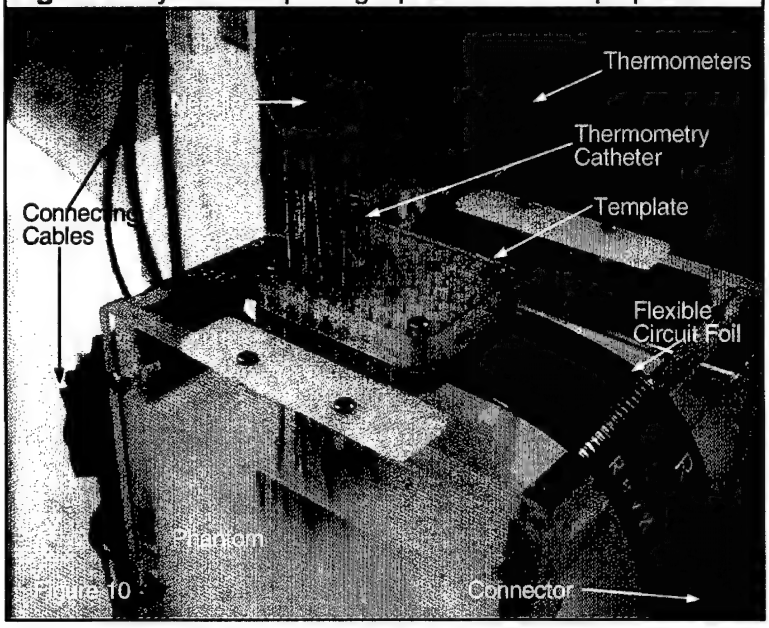

Figure 10

As stated in the grant application itself, no changes to the hardware were necessary to accommodate HDR templates other than the redesign of the template itself. Consequently the majority of testing was software related and concentrated on various failure modes that might compromise patient safety. The following situations were tested under a variety of conditions:

- PS program lockup.
- TS program lockup
- MC program lockup
- PS/TS computer failure.
- MC computer failure.
- Network communication failure
- Various cable disconnects.

In all instances the simulated failure resulted in the removal of power from the template and placed the system in a safe mode. Some of the failures resulted in power shutoff on the treatment computer. Disconnecting the cables to the template eliminated power deposition, which was detected by the computer program (PS).

Task 4. Recruit and treat patients with recurrent prostate cancer that meet the patient selection criteria outlined in the approved clinical protocol.

Figures 11 to 12 show a patient under treatment with the system developed and tested in Tasks 1-3. The implant consisted of 13 hyperthermia/brachytherapy needles and 5 thermometry catheters with a total of 30 temperature points in five tracks inserted into the catheters.

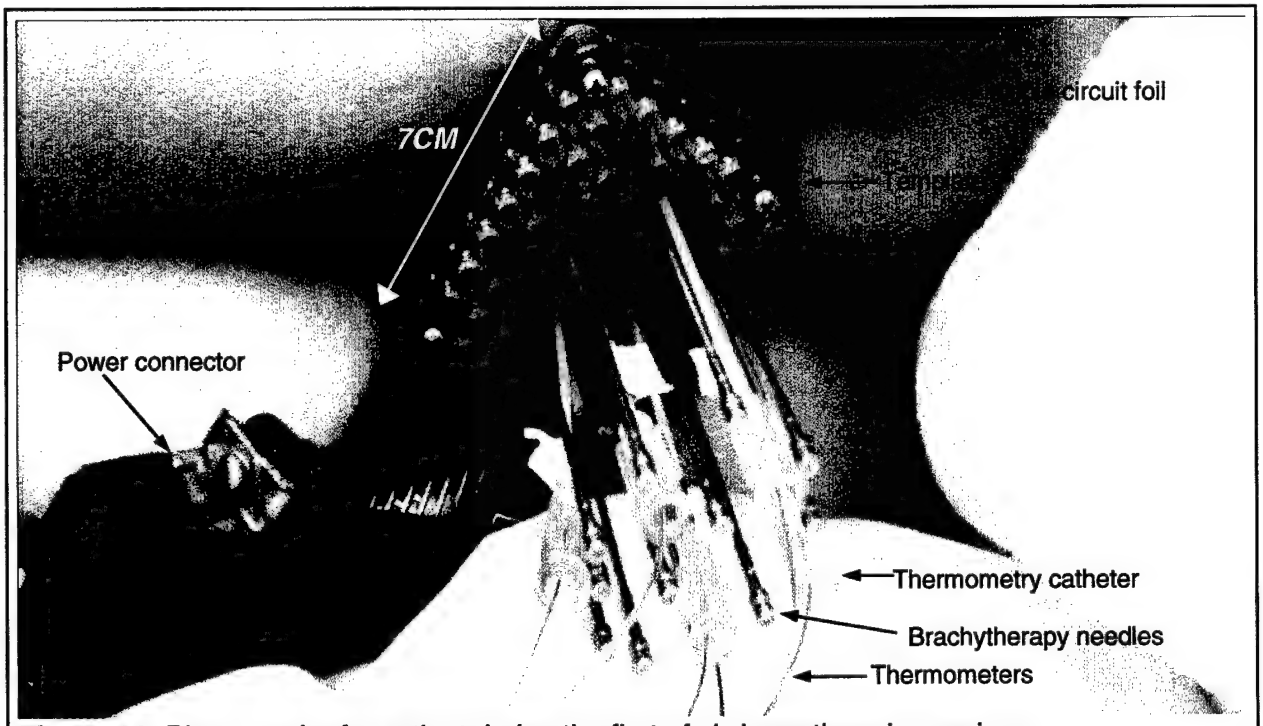

Figure 11: Photograph of a patient during the first of six hyperthermia sessions.

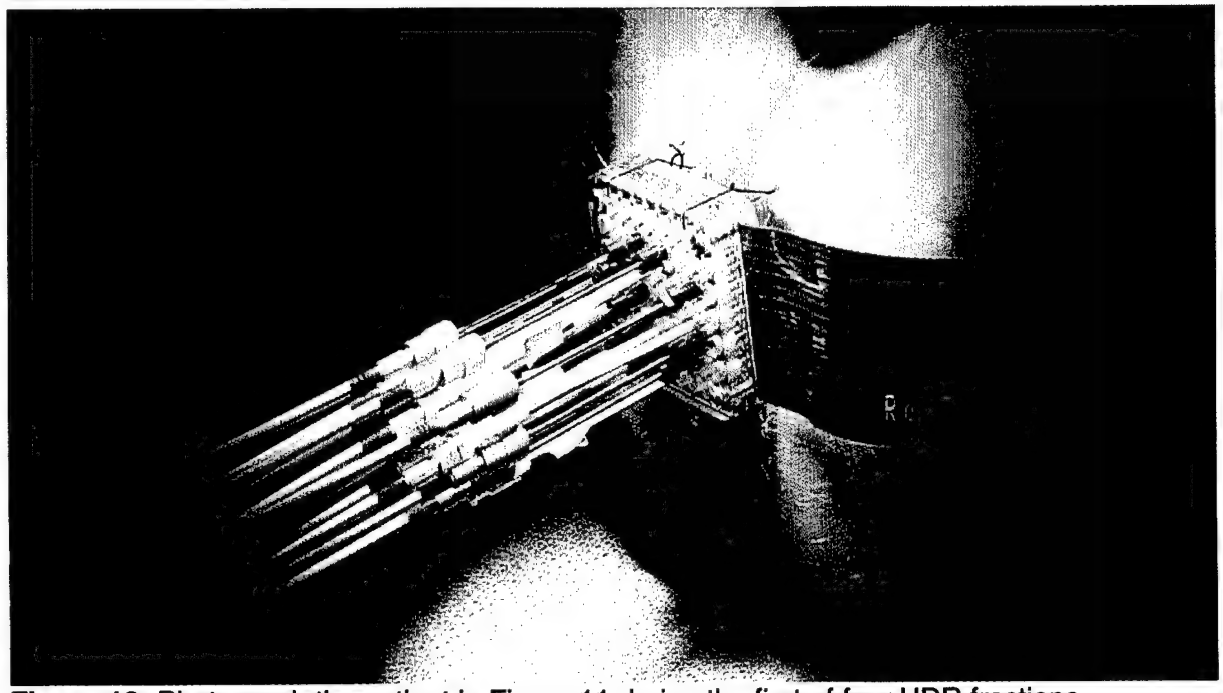

Figure 12: Photograph the patient in Figure 11 during the first of four HDR fractions.

The treatment regimen was as follows:

Day !:	Implant procedure
	3 hours hyperthermia
	7Gy HDR fraction
	3 hours hyperthermia
Day 2:	3 hours hyperthermia
	7Gy HDR fraction
	6 hours hyperthermia
	7Gy HDR fraction
	3 hours hyperthermia
Day 2:	3 hours hyperthermia
	7Gy HDR fraction (total dose delivered: 28Gy)
	Remove implant and discharge if appropriate.

During the first hour of treatment no analgesia is administered and power is raised slowly to determine tolerance and whether or not significant pain toxicity is encountered. If tolerance is good, pain toxicity is non-limiting, then epidural analgesia is started and continued for the duration of the treatment, slightly less than 2 days. If pain toxicity is encountered the remainder of the treatment is performed using patient controlled intravenous analgesia (PCA). The temperature target is a T_{80} of 41°C. This means that 80% of the measured intratumoral temperature points should be at or above 41°C. The data of Figure 13 show that this target was achieved and sustained for this patient. Similar heating patterns were achieved during subsequent hyperthermia sessions with a more rapid rise during the first hour.

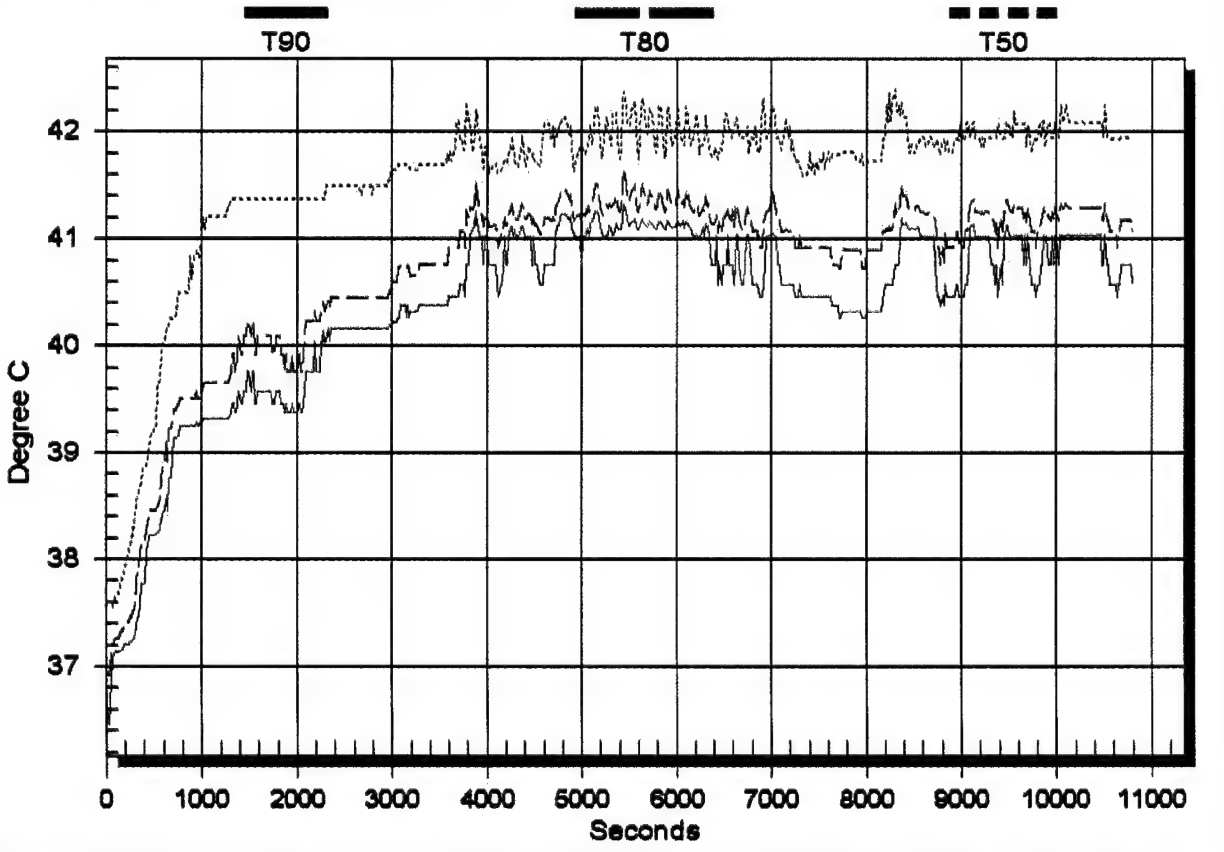

Figure 13:.Temperature parameters for the three hour duration of the first hyperthermia session for the patient shown in Figure 11. The data are for 21 intratumoral temperature points.

Task 5. Investigation and integration of gene therapy into the treatment scheme.

The research effort for gene therapy was directed towards producing adenovirus vectors that require both ionizing radiation and heat shock to produce the therapeutic transgene. One reason for doing this was the inability to create heat shock inducible adenovirus vectors for all cytotoxic genes except the cytolethal distending toxin B (CdtB). This problem occurs because the truncated HSP70 B promoter is leaky in the HEK 293 human endothelial cells used to produce the adenovirus vectors and leak-through expression of the toxic transgene is sufficient to kill the 293 cells before they can produce the viral vectors. The CdtB adenovirus vectors could be made because CdtB is a slow acting toxin that did not kill the cells before virus production was completed.

Another reason for producing this double-trigger expression system is to address concern over unsolicited expression of cytotoxic transgene under control of only one promoter. The most concern has been raised over cytotoxic transgene expression from the heat shock promoter in the event that an animal or patient develops a fever sufficient to induce the heat shock promoter.

The double trigger expression system pictured in Figure 14 below eliminates both of these problems. The problem of adenovirus production is solved because the cytotoxic transgene cannot be expressed within the 293 cells unless they are irradiated to remove the stop-transcription sequence downstream of the heat shock promoter. Hence, viral production can proceed as with a noncytotoxic transgene. We have found that leak-through CRE expression

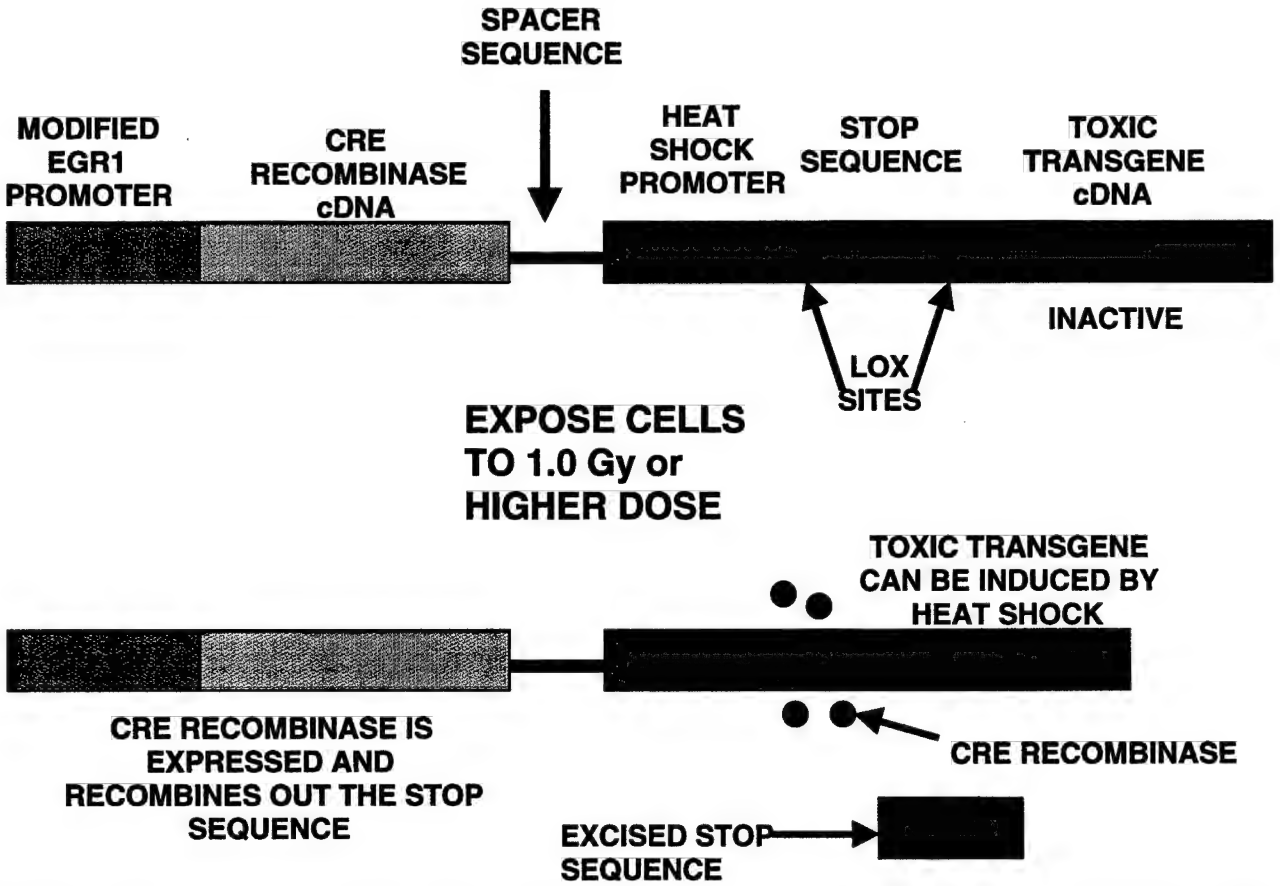

Figure 14: Diagram of the double switch stress controlled promoter that has been constructed for the application of toxic transgenes to combined modality clinical therapy.

from the modified EGR1 promoter is not sufficient to recombine out the stop sequence, and this result agrees with that of others using this promoter (e.g. Scott et al. 2000).

After delivering the adenovirus vectors to a tumor, the cytotoxic transgene will only be expressed within tissues that receive both irradiation with 1.0 Gy or more and a heat shock at 41.0°C or higher. The radiation exposure induces CRE recombinase expression that is sufficient to recombine out the stop sequence and arm the heat shock promoter. Subsequent heat shocks can be used to control cytotoxic transgene expression from the heat shock promoter, but only within the irradiated tissue volume. Cytotoxic transgene expression cannot occur outside of the irradiated tissue volume, even if the animal or patient develops a fever, because the heat shock promoter has not been armed.

All of the DNA constructs have been made, except that the cytotoxic transgene has been replaced with enhanced green fluorescent protein (EGFP) for testing purposes. The DNA constructs are currently being transferred into plasmids that will be used to produce recombinant deficient adenovirus vectors. Once the double promoter adenoviruses with the EGFP reporter have been tested adenoviruses containing the cytotoxic transgenes will be constructed.

Key Research Accomplishments: Year One

- A hyperthermia template compatible with high dose rate brachytherapy (HDR) was constructed and tested.
- Software was written and tested which is compatible with the quasi-random needle placement used in HDR.
- The combination of the new template and software underwent extensive testing using phantoms to qualify the system for use in patient therapy.
- A patient was treated using the system was treated according the the approved protocol for this project.
- A combination promoter system that is activated by ionizing radiation and hyperthermia was constructed for use in gene therapy. This promoter system is to be used to construct vectors that contain cytotoxic genes (e.g. the cytolethal distending toxin).

Reportable Outcomes: Year One

One abstract was published in the proceedings of the annual meeting of the North American Hyperthermia Society and the Radiation Research Society at Reno Nevada, April 20-25, 2002.

> Thermal Goals for Gene Therapy. Corry, P.M., Borrelli, M.J., and Armour, E.P.: Presented as part of a symposium entitled Defining Thermal Goals for Hyperthermia. (copy appended)

Another presentation was made at the Reno meeting in another symposium entitled Interstitial Hyperthermia Update, however due to an error in the abstract submission system no abstracts were published for this symposium. A copy of the program page from the meeting and the title page from the presentation file are appended.

> RF Interstitial for Combined Thermobrachytherapy. Corry, P.M., Martinez, A., Gersten D. and Armour, E.P.

In preparation:

A manuscript entitled An Advanced System for Combining Hyperthermia and brachytherapy for Pelvic Tumors.

Conclusions: Year One

- The new HDR template was constructed and works as anticipated. Some cracking difficulties were encountered with the original plastic components constructed of Lucite but a switch to another plastic Delrin solved the problem.

- The software as written and extensively tested is ready for patient therapy. It is anticipated that some modifications will be necessary after further experience is gianed with actual patient therapy.

- One patient was treated during this granting period. The patient tolerated the procedure well and the target temperature parameters were achieved. The patient, to date (4 months follow-up), has shown no significant short term toxicities and his PSA has decreased to zero from a pretreatment value of 5.4. Obviously, the follow-up period is short and no conclusions can be drawn on long term tumor control and late toxicities. The results indicate that we are now ready for continued patient accrual under the protocol.

- The gene therapy project is progressing well and we are now prepared to proceed with vector construction using the heat and ionizing radiation induced promoter. Cytotoxic transgenes can be added to the construct (e.g. CdtB and Diphtheria) and subsequently testing can begin in *in vitro* and rodent model systems.

- "So what". The combination of the progress to date suggests that this approach may result in a viable treatment for recurrent prostate cancer. Whether or not that is true will require several years more work.

References

Scott, S.D., Marples, B., Hendry, J.H., Lashford, L.S., Embolton, M.J., Henter, R.D., Howell, A. and Margison, G.P.: A radiation-controlled molecular switch for use in gene therapy of cancer. Gene Therapy, 7(13):1121-1125, 2000.

Appendices

A copy of the program page for the Gene Therapy presentation referred to in the Reportable results section

A copy of the published abstract for the Gene Therapy presentation referred to in the Reportable results section.

A copy of the program page for the Interstitial Hyperthermia presentation referred to in the Reportable results section

A copy of the the first page of the presentation file for the Interstitial Hyperthermia presentation referred to in the Reportable results section

ing has been successfully correlated with dose and volume parameters (Sem Rad Onc 11:215, 2001; IJROBP 49:685, 2001; IJROBP 47:103, 2000). Investigators at the University of Pittsburgh have pioneered single fraction radiosurgery for benign and malignant brain lesions in the U.S. In patients with arteriovenous malformations, the risk of RT-induced brain injury is related to the region of brain irradiated, as well as the volume of brain irradiated to 12 Gy (IJROBP 46:1143, 2000; 40:273, 1998; 38:485, 1997). Investigators at the University of Michigan have aggressively studied radiation-induced liver injury in a volume-dependent dose escalation study. They have successfully related clinical liver injury to dose and volume parameters (IJROBP 31:883, 1995; 31:1237, 1995; JCO 16:2246, 1998). Investigators at Duke University have studied regional and whole lung consequences of thoracic radiation, as well as dose escalation for unresectable tumors. They, and others, have related the risk of clinical pneumonitis to DVH-based parameters such as the mean lung dose (IJROBP 51:650, 2001; 33:455, 1995; 45:323, 1999; 42: 1, 1998).

9:00 AM **(S06-1)** Volume effects in late rectal bleeding after external beam radiotherapy for prostate cancer.

A. Jackson[1]. [1]Department of Medical Physics, Memorial sloan Cancer Center, 1275 York Avenue, New York, New York 10021

9:30 AM **(S06-2)** Volume effects on tolerance to stereotactic radiosurgery.

J.C. Flickinger[1]. [1]Department of Radiation Oncology, University of Pittsburgh School of Medicine, 200 Lothrop Street, B-300, Pittsbugh, PA 15213

10:00 AM **(S06-3)** Dose-Volume Tolerance of the Liver to Radiation.

L.A. Dawson[1,*]. [1]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI 48109

10:30 AM **(S06-4)** Fractal analysis and volume effects in radiation-induced lung injury.

Z. Vujaskovic[1,*], O. Craciunescu[1,*] and L.B. Marks. [1]Duke University Medical Center, Department of Radiation Oncology, Durham, NC 27710

9:00 AM to 11:00 AM
Sunday, April 21, 2002
NAHS Symposium 7
Room: Nevada 4-5

Chair: J.L. Roti Roti

NAHS Defining Thermal Goals for Hyperthermia

L.R. Prosnitz[1,*], J. Roti-Roti[2,*], M.W. Dewhirst[1,*], P. Wust[3,*] and P. Corry[4,*]. [1]Duke University Medical Center, Dept. Radiation Oncology, Durham, NC 27710. [2]University of Washington, Department of Radiation Oncology, St. Louis, MO. [3]Charite-Campus Virchow Klinikum, Dept. Radiation Oncology, Augustenburger Platz 1, Berlin, Germany 13353. [4]William Beaumont Hospital, Radiation Oncology, Royal Oak, MI 48073.

A critical objective of clinical hyperthermia (HT) is to gain an understanding of what constitutes an optimal HT treatment course, i.e. establish thermal goals. Historically, temperatures in the range of 42 to 43°C were thought necessary to reliably achieve cytotoxicity or sensitization to radiotherapy (RT) or chemotherapy (CT), that such temperatures needed to be maintained for 45-60 minutes and that multiple courses had to be given. In practice, such temperatures are seldom achieved, particularly for deep-seated tumors heated with external power sources. Despite this, multiple phase II and III clinical trials demonstrate some success for HT. The challenge for both biologists and clinicians is to explain these successes, create the conditions where they can be reproducibly achieved, and explore new areas of cancer biology where the kinds of temperatures and thermal doses achieved in the clinic may be of value. These subjects will be addressed by the speakers in this symposium. Professor Joseph Roti-Roti will address the "Biology of simultaneous and sequential moderate HT." The St. Louis group has interest in the simultaneous application of HT and RT. Both laboratory and clinical studies demonstrate apparent radiosensitization with comparatively modest temperatures of 41°C. Professor Mark Dewhirst at Duke will speak on "Therapy specific thermal goals." He will address the exciting new areas of liposome encapsulated CT and gene therapy, the role of HT in increasing the effectiveness of these new therapies, and the necessary thermal goals. In preclinical studies, modest temperature elevations likely achievable in the clinic, appear to provide synergy. Professor Peter Wust will speak on "Deep HT thermometry and thermal dose goals." He will update the analysis of the German pelvic and rectal trials correlating thermal parameters with response and outcome. He and the group at Duke are making meaningful advances in non-invasive thermometry in an attempt to achieve detailed and accurate three-dimensional thermal mapping. Some of these results will be shown. Finally, Professor Peter Corry will address "Gene therapy activation heat dose." His group at William Beaumont Hospital has done exciting work in this area where again comparatively modest doses of heat may successfully turn on therapeutically important genes.

9:00 AM **(S07-1)** Radiosensitization of Human Tumor Cells by Moderation Hyperthermia—Considerations for Thermal Goals.

J.L. Roti Roti[1], M. Xu[1,*], E. Moros[1,*], R. Myerson[1,*] and W. Straube[1,*]. [1]Division of Radiation and Cancer Biology, Washington University School of Medicine, St. Louis, Mo 63108

9:30 AM **(S07-2)** Defining thermal goals for hyperthermia.

P. Wust[1,2], J. Gellermann[2], B. Hildebrandt[1], B. Rau[2], R. Felix[1,2] and P. Schlag[2]. [1]Charité Medical School - Campus Virchow-Klinikum, Berlin, Germany 13353, [2]Charité Medical School - Robert-Rössle-Klinik, Berlin, Germany 13125

10:00 AM **(S07-3)** Thermal goals for gene therapy and liposomal drug delivery.

M.W. Dewhirst[1,*], C.Y. Li[1,*] and G. Kong[1]. [1]Department of Radiation Oncology, Duke University Medical Center, Durham, NC 27710

10:30 AM **(S07-4)** Thermal Goals for Gene Therapy.

P.M. Corry[1], M.J. Borrelli[1,*] and E.P. Armour[1,*]. [1]Radiation Oncology Research Laboratories, William Beaumont Hospital, 3601 W. 13 Mile Rd., Royal Oak, MI 48073

Plenary Lectures

11:15 AM to 12:15 PM
Sunday, April 21, 2002
Plenary Lecture 2
Room: Tahoe

Introducer: G. Iliakis

Double-strand Break Repair in Human Cells

S. West[1]. [1]Imperial Cancer Research Fund, Clare Hall Laboratories, South Mimms, Herts., UK EN6 3LD.

DNA double strand breaks can be repaired by homologous recombination or by non-homologous end-joining. In

events as opposed to lethal events that require and interaction between two separate energy deposition events. This result has important implications for combining moderate hyperthermia with fractionated radiotherapy. To gain insight into the mechanism of radiosensitization by moderate hyperthermia we measured the effect of 41.1oC hyperthermia on the intracellular localization of the DNA double strand break repair protein, Mre11, using in situ immunofluorescence and immunoblotting of soluble and insoluble cellular fractions. The results showed that Mre11 delocalizes from the nucleus as a function of time at 41.1oC. We then determined if 41.1oC hyperthermia altered the association of Mre11 with its functional partner, Rad50. A significant decrease in the amount of Rad50 recovered with Mre11 occurred under the experimental conditions that produced significant radiosensitization. These results are consistent with the possibility that the heat-induced perturbation in Mre11 localization and its radiation-induced association with Rad50 contributes to an increase in radiosensitivity.

Support NCI Grants CA75556 and CA43198.

(S07-2) Defining thermal goals for hyperthermia. P. Wust[1,2], J. Gellermann[2], B. Hildebrandt[1], B. Rau[2], R. Felix[1,2] and P. Schlag[2]. [1]Charité Medical School - Campus Virchow-Klinikum, Berlin, Germany 13353. [2]Charité Medical School - Robert-Rössle-Klinik, Berlin, Germany 13125.

Temperatures postulated from preclinical studies (42-43 C) are, at least in parts of the tumor, clearly not obtained under clinical conditions and, therefore, according to the 43 deg-C-dogma the general effectiveness has been questioned. However, a number of randomized studies were nevertheless positive. Inspecting these studies in more detail, in the hyperthermia arm subgroups of patients with better heating can be specified - and better heating is correlated with better response, local control or even survival. In our own rectal cancer study (116 pts.) we applied a preoperative regimen with radio-chemotherapy +/- hyperthermia, and found better response in the hyperthermia arm (CR+PR 66% vs. 51%) and conversely a higher percentage of progressive disease in the non-hyperthermia arm (PD 7% versus 0%). In particular, we found in the responder group a much higher percentage of patients with T90 $>$ 40.5 C and cum min (T90*40.5 C) $>$ 30 min (82% vs. 59%). However, thermal parameters which are correlating with effectiveness can vary from study to study. In case of chest wall recurrences Sherar 1997 found the minimum thermal dose in the tumor-related measurement points as predictive parameter, in case of malignant melanoma lesions Overgaard 1996 found the cumulative maximum thermal dose as predictive. In phase II-studies various other thermal parameters were found: e.g. 43 C-equivalent minutes T90, T90 and others. On summary, it appears that a minimum temperature of 40.5 C for several sessions (amounting to at least 30 min) might be sufficient for an effective hyperthermia course. In conclusion, concepts to improve temperature distributions and, therefore, effectiveness of regional hyperthermia are needed. Recently, thermal data were achieved by using minimal invasive thermometry in the rectum, bladder or cervix. If carefully evaluated, an equivalent relationship is obtained with these thermal data. Much better preconditions are given in a hybrid system where MR-temperatures are registered during heating simultaneously. In phantom measurements a temperature accuracy of better than +/- 1 deg-C has been achieved. Temperature-related MR data sets during RHT were achieved. Latest results show, that we can expect now even better (three-dimensional) predictors to assess heating quality and clinical outcome.

P. Wust, scientific cooperation with BSD Corp.

(S07-3) Thermal goals for gene therapy and liposomal drug delivery. M.W. Dewhirst[1,*], C.Y. Li[1,*] and G. Kong[1]. [1]Department of Radiation Oncology, Duke University Medical Center, Durham, NC 27710.

Most of the concepts regarding thermal dosimetry arose from in vitro and in vivo thermobiologic studies done in the late 1970's and early 1980's, where the goal was to kill cells with hyperthermia. The well known Arrhenius relationship shows that the rate of cell killing doubles or quadruples for every degree the temperature is increased, depending on whether one is above or below 43°C and also whether one is dealing with human or rodent cell lines. To achieve reasonable levels of cell killing temperatures exceeding 42°C for an hour or more are needed. When one is using hyperthermia to increase gene expression via the heat shock promoter or to increase liposomal drug delivery, however, the thermal goals are significantly lower. For example, with the heat shock promoter, significant levels of gene expression can be seen with 40°C for an hour. The thermal threshold for increased liposomal extravasation from microvessels has also been shown to be 40°C. The rate of extravasation doubles for each degree achieved above 40°C. When temperature sensitive liposomes are used temperatures near 40°C may be sufficient, however, particularly if one uses low temperature sensitive liposomes. Work supported by grants from the NIH/NCI CA42745 and CA 81512.

Consultant, Celsion Corporation

(S07-4) Thermal Goals for Gene Therapy. P.M. Corry[1], M.J. Borrelli[1,*] and E.P. Armour[1,*]. [1]Radiation Oncology Research Laboratories, William Beaumont Hospital, 3601 W. 13 Mile Rd., Royal Oak, MI 48073.

Effective gene therapy is one of the most sought after goals of modern medical research. At the present time most forms of gene therapy introduce the desired transgene on a constitutive, always on to some degree, promoter with the hope that other physiological factors will modulate expression of the transgene's gene product. One of the most exquisitely controlled promoters available is the human HSP70 promoter which is virtually silent in the absence of heat shock. After even mild thermal exposure (41 deg. C for 30 minutes) high levels of transcription of transgenes can be detected, will persist for a few hours and then spontaneously shut down as the production of heat shock factor (HSF) decreases at physiologically normal temperatures. The thermal target for controlling heat activated gene therapy depends on the target cell type, the desired level of gene expression and the desired length of time for transgene expression. To some extent these parameters are altered by cell cycle position at the time of thermal exposure which may have important implications in clinical application to tumor therapy. Another important influence on thermal goals in the context is other agents, such as ionizing radiation, with which gene therapy is being combined in human applications. Elevated temperatures are known to enhance ionizing radiation by at least two distinct mechanisms, repair inhibition and reoxygenation, which themselves have differing thermal goals. Higher temperatures or longer times being required for repair inhibition. Hyperthermia may also be desirable in enhancing the effects of the transgene's gene product and those thermal goals may be different than for the activation of transgene transcription. Other factors which will be discussed are the incorporation of reporter genes that might be picked up as tracers with MRI of PET procedures to dynamically assess efficacy of transgene activation on three dimensions and methods for conformal delivery of the activation heat shock. Other factors may be the combination with other promoters such as those activated by ionizing radiation and hypoxia.

(S08-1) Role of DNA-PK in the repair of DNA double-strand breaks after irradiation. G.C. Li[1,*], H. Ouyang[1], S. Wang[1], A. Kurimasa[2] and D.J. Chen[2]. [1]Memorial Sloan-Kettering Cancer Center, New York, NY 10021. [2]Lawrence Berkeley National Laboratory, Berkeley, CA 94720.

Among the various forms of DNA damage, DNA double-strand breaks (DSBs) are potentially the most lethal. DSBs can be produced by ionizing radiation, and can also arise endogenously as intermediates of DNA rearrangement during certain biological processes, such as meiosis, V(D)J recombination in early lymphocyte development, and class switch recombination in mature B cells. If unrepaired, DSBs likely result in cell lethality; if repaired incorrectly, they can lead to mutations. Recently, genes involved in DSB repair, including *Ku70, Ku80* and *DNA-PKcs* have been identified, and knockout mice and cell lines have been generated. The roles of these repair genes and the molecular processes in DNA repair, lymphocyte development and tumorigenesis will be discussed.

J.R. Lepock[1,*]. [1]Departments of Physics and Biology, University of Waterloo, Waterloo, Ontario N2L 3G1

4:15 PM **(MS09-2)** Role of intranuclear sorting of denatured proteins during stress for their subsequent fate upon stress-relief.

H.H. Kampinga[1,*]. [1]Dept. of Radiation and Stress Cell Biology, Div. Cell Biology, Faculty of Medicine, University of Groningen, A. Deusinglaan 1, Building 3215, 5th Floor, Groningen, The Netherlands 9713AV

4:45 PM **(MS09-3)** TBD

M. Borrelli, Dept. of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI

At the time of publication, no abstract was available.

3:45 PM to 5:15 PM
Monday, April 22, 2002
NAHS Mini-Symposium 10
Room: Nevada 4-5

Co-Chairs: P. Sneed and I-C. Hsu

NAHS Interstitial Hyperthermia Update

P.K. Sneed[1,*]. [1]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA 94143.

Interstitial hyperthermia holds promise to extend the applicability of hyperthermia to many more tumor sites and types than are amenable to superficial hyperthermia. In addition, interstitial methods may allow more control over heating patterns than is generally possible with superficial or regional techniques. This mini-symposium includes talks from active investigators of interstitial hyperthermia and brachytherapy. Dr. A. M. N. Syed will present data from his experience using interstitial microwave and radiofrequency hyperthermia for head and neck cancers and a variety of pelvic malignancies at Long Beach Memorial Medical Center over the past two decades and Dr. D. J. Lee will give an overview of the Johns Hopkins' interstitial thermoradiotherapy experience.

3:45 PM **(MS10-1)** Interstitial Microwave Hyperthermia for Head & Neck Cancer.

A.M.N. Syed, Long Beach Memorial Center, Long Beach, CA

At the time of publication, no abstract was available.

4:05 PM **(MS10-2)** Microwave Interstitial Hyperthermia.

D. Lee[1,*]. [1]Division of Radiation Oncology, The Johns Hopkins Hospital, 401 N Broadway, Baltimore, MD 21231

4:25 PM **(MS10-3)** Interstitial Radiofrequency Hyperthermia for Pelvic Malignancies.

A.M.N. Syed[1]. [1]Long Beach Memorial Center, Long Beach, CA

At the time of publication, no abstract was available.

4:45 PM **(MS10-4)** RF Interstitial for Combined Thermo-brachytherapy.

P. Corry[1]. [1]Dept. of Research, William Beaumont Hospital, Royal Oak, MI

At the time of publication, no abstract was available.

5:00 PM **(MS10-5)** Interstitial Ultrasound Hyperthermia: Preliminary Clinical Experience.

C.J. Diederich,[1] W.H. Nau,[1] J. Hsu,[1] P.K. Sneed[1]. [1]University of California, San Francisco, CA

At the time of publication, no abstract was available.

5:30 PM to 6:30 PM
Monday, April 22, 2002
Plenary Lecture 5
Failla Lecture
Room: Tahoe

Research in Radiation Biology and Physics

J.F. Fowler[1]. [1]Dept of Human Oncology, University of Wisconsin, Madison, WI 53792.

I changed my career from Radiation Physics to Radiation Biology in the 1960's when I found that the uncertainties in Radiation Biology were ten times larger than those involved in physics measurements. There had to be some uncertainties which Radiation Biologists could help to narrow down. In spite of plenty of biological uncertainties still remaining, there has been progress in understanding some aspects of radiation biology applied to the treatment of cancer, and even some practical progress in better treatments for certain cancer sites. When should short schedules be used, and what are their limitations? What are the influences of early reactions on the late reactions of normal tissues? We've learnt that the proliferation status of cells in a tissue have a powerful effect on the response of the tissues, sometimes overarching the subleties of cytokines and bioinformatics, and that certain types of tumor need to be treated with the opposite of our previous strategies. After a generation when we were taught that "little and often" was an ideal treatment modality, we are now learning circumstances in which fewer and larger doses can have advantages.

6:30 PM to 8:00 PM
Monday, April 22, 2002
Failla/Robinson Reception
Room: Reno Ballroom

HDR Thermobrachytherapy

Peter Corry
Alvaro Martinez
David Gersten
Elwood Armour

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